INDOOR NITROGEN OXIDES*

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Health effects due to indoor nitrogen dioxide levels have become particularly controversial. This controversy exists not only because, as described below, results of studies as to whether respiratory effects are associated with nitrogen dioxide levels derived from gas stoves differ, but because this question is important to the standard-setting process for outdoor air. This latter is literally a multibillion dollar question about which there has been more than the usual difficulty in obtaining scientific evidence. For the most part, this reflects the dual source of outdoor nitrogen oxides: automobile emissions and high temperature stationary source fossil fuel combustion, such as from power plants. Accordingly, outdoor exposure to nitrogen dioxide is usually associated with other major pollutants and it is therefore difficult to disentangle nitrogen dioxide effects from those due to other respiratory irritants. In contrast, the combustion process in gas stoves is relatively clean and there are fewer competing variables.

The precursors of oxides of nitrogen present indoors or in the general environment are for the most part simply the oxygen and the nitrogen in the atmosphere. These can be united in flames or by other means, including electric arcs, but not simply by the heat of an electric grill. Accordingly, gas stoves can produce substantial quantities of oxides of nitrogen while electric stoves in essence do not. With a flame, generally the

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hotter the temperature the greater the likelihood of formation of oxides of nitrogen. Nitric oxide (NO) is usually formed first and in greater amounts than the higher oxidation state nitrogen dioxide (NO_2). Nitric oxide is readily oxidizable in the atmosphere to nitrogen dioxide. In itself, nitric oxide is relatively harmless as compared to nitrogen dioxide, and present evidence indicates that only the latter need be considered in terms of air pollutant health effects.

Nitrogen dioxide is a pulmonary irritant which at high levels produces death in pulmonary edema. Of the various effects observed at lower pollutant levels, undoubtedly the most thoroughly studied is that of the potentiation of bacterial respiratory tract infections.[1-6] This was originally noted by Ehrlich and his colleagues in a series of studies in which the number of mice dying following inhalation of a pneumonia-provoking aerosol of *Klebsiella pneumoniae* was increased by exposure to nitrogen dioxide. The effect was observed at levels of approximately 3.5 parts per million (ppm.) or higher nitrogen dioxide following acute exposure, and as little as 0.5 ppm. nitrogen dioxide following long-term exposure. This enhancement of respiratory tract infections by nitrogen dioxide was observed by Ehrlich's group in primates as well.[3] Further evidence for this effect comes from the fact that it has been observed in other laboratories,[4-6] and is supported by various mechanistic studies. The latter have shown interference in the antibacterial defenses of the lung following nitrogen dioxide exposure [2,6] and, more recently, a specific decrement in the ability of rat lung alveolar macrophages to produce superoxide anion radical, a species active in bactericidal effects.[7] There is thus convincing evidence that inhalation of reasonably low levels of nitrogen dioxide is capable of potentiating bacterial infections in the lung. Before discussing studies evaluating the respiratory health effects of indoor nitrogen dioxide, two further points should be made. First, episodes of acute respiratory infection in man, which are frequently measured in such studies, reflect primarily a viral process, while the evidence described above concerns bacterial infections in animals. Whether nitrogen dioxide exposure potentiates viral infections is still uncertain. Second, recent studies suggest that short-term peak levels of nitrogen dioxide are much more important than average levels in potentiating respiratory tract bacterial infections in animal models. Exposure to nitrogen dioxide within a kitchen is in fact characterized by high short-term peaks due to the use of the stove in cooking. However, thus far studies relating health effects to nitrogen dioxide have looked only at average levels rather than peaks. Peak levels over gas stoves of higher than 1 ppm. have been reported[8] and average kitchen levels frequently exceed the allowable United States outdoor standard of 0.05 ppm.[8-10]

Three major sets of studies will be considered in this review: those by Keller et al.,[11,12] Speizer et al.,[13,14] and Melia et al.[10,15-18]

No evidence of a difference in the extent of respiratory tract dysfunction between those living in homes with gas or with electric stoves was noted by Keller et al.[11,12] These studies, sponsored by the American Gas Association, were performed in upper middle class homes in Columbus, Ohio. In the initial studies, families living in 441 separate homes were enrolled in a one-year program in which they were questioned by telephone every two weeks concerning episodes of acute respiratory disease. Gas stoves were present in 232 of these homes while the remaining had electric cooking equipment. Nitrogen dioxide monitoring performed in a random sample of 83 gas-cooking households revealed a mean of 0.05 ppm. (range 0.01-0.11 ppm.), while in 50 electric-cooking households the mean NO_2 level was 0.02 ppm. (range 0-0.06 ppm.). No difference in the number of episodes of respiratory tract infection was observed between parents or children living in the gas homes as compared to parents and children living in the electric homes. Similarily, no significant effect of cooking fuel was observed in pulmonary function testing performed in 42% of the sample. Dr. Keller and his group also obtained questionnaire data from the Environmental Protection Agency's CHESS Studies on homes in Riverhead, Long Island, in which, again, they found no statistically significant difference in respiratory illness rates between mothers living in homes with electric and gas stoves. Keller et al. performed a follow-up study of demographically matched families living in 60 gas-cooking homes and 60 electric-cooking homes from their study population in Columbus, Ohio.[12] This used a much more intensive approach in that any positive response from the the biweekly telephone questionnaire was followed up by a visit from a nurse-epidemiologist. During this visit the family member said to be affected was interviewed and examined as were other family members. Again, no consistent significant differences were observed in acute respiratory illness incidence between gas-cooking and electric-cooking households.

Bouhuys and his colleagues also reported no difference in acute respiratory disease incidence between gas and electric-cooking homes in two communities. However, this study was primarily aimed at evaluating outdoor air pollution and contained relatively few children in the population tested.[19,20]

Speizer et al. studied the effects of cooking with gas versus electricity as part of an extensive evaluation of air pollution effects in six cities.[13,14] A total of 8,120 white children, 6 to 10 years old, were included in the protocol. Historical data on illness, obtained from questionnaires filled out by the parent, were used to obtain information concerning whether the child had had a serious respiratory disease before age two, whether the child had had a respiratory illness in the past year, and whether a physician had diagnosed the child as having bronchitis. In addition, pulmonary function was measured in each child. Information about the home-cooking device, heating fuel, the presence of adult smokers, and air conditioning was also obtained, and reported disease rates were analyzed using log-linear models to determine significant interaction among the variables. No effect of home-heating fuel or the presence of air conditioning was observed. Social class, parental smoking, and type of cooking stove had variable effects on the reported disease rates.

Of particular note was an association between rates of illness before age two and gas stoves in the home. This was not accounted for by smoking or by social class, but it did depend upon recall of what had happened four to eight years earlier. Small but statistically significant lower levels of pulmonary function (FEV_1,FVC) were also observed in children from households with gas stoves. Of particular note is the relative consistency of these findings across each of the six cities which were studied.

The most extensive studies evaluating the possible relation of cooking with gas to respiratory disease has been performed by the Department of Community Medicine at St. Thomas' Hospital Medical School in England. As part of a national study of respiratory illness among young schoolchildren, this group originally reported a high prevalence of respiratory symptoms and diseases in children living in homes with gas stoves in comparison to children in homes with electric stoves in 1973. This study evaluated a total of 5,768 children from 28 randomly selected areas of England and Scotland. Among positive associations with gas stoves were cough, colds going to the chest, and bronchitis. This effect did not appear to be accounted for by social class, age, family size, and levels of outdoor air pollution. However, no information was obtained concerning adult cigarette smoking in the house, a known factor in childhood respiratory disease.[15]

In a subsequent follow-up, longitudinal data were collected over the four following years of the study. Results were reported for two groups of children: those aged five to 10 who were present in 1977 in the study group but not 1973, and those present in 1973 who were followed up in subsequent years. In this 1977 study, information was collected as to the number of people who smoked tobacco in the home. Again, the prevalence of one or more respiratory symptoms or diseases was higher in children from homes where gas was used for cooking than in homes where electricity was used. The association appeared to be independent of the number of cigarette smokers in the home. There was some indication that the effect decreased as children grew older.

Both of these studies, as well as those of Keller et al. and Speizer et al., described above, depend solely upon a comparison between the presence of gas or electric stoves. As a number of factors, including raised levels of NO_2, could explain the association between respiratory illness and gas cooking, the results of these studies provide only indirect evidence that NO_2 may be harmful to health. To investigate whether NO_2 is the cause of the association, a study in which nitrogen dioxide levels are actually measured in each home is required. In a study of respiratory effects in school children and their families in which this reviewer participated, Palmes monitors were used to measure mean weekly indoor nitrogen dioxide levels in 515 homes in a predominantly lower class area of Middlesborough, England.[10] The monitor is a three-inch-long acrylic tube with a wire mesh impregnated with triethanolamine in a cap at the bottom.[9] The amount of NO_2 trapped is a function of the integrated mean concentration of NO_2 in the atmosphere and the time that the top of the tube is open. Mean NO_2 levels in 428 homes with gas stoves in Middlesborough was 0.112 ppm., while that in 87 kitchens with electric stoves was 0.018 ppm. Other findings included a mean NO_2 level in the bedrooms of 107 children where gas was used for cooking of 0.031 ppm., while in 18 bedrooms from electric stove homes it was 0.014 ppm. For comparison purposes, outdoor levels in 75 sites in the area ranged from 0.014 to 0.024 ppm.

Study of the relation of nitrogen dioxide levels to lung function and respiratory illness in six to seven-year-old school children living in these homes provided no clearcut results. Lung function was not related to levels of kitchen or bedroom nitrogen dioxide. However, there was a tendency toward an increased prevalence of respiratory illness in children from homes with gas as compared to electric stoves ($p=0.10$) and the symptoms were directly related to bedroom, but not kitchen, nitrogen dioxide levels. A possible compounding variable in these studies is dampness, which has been suggested to be greater in gas stove homes because of water vapor in natural gas. However, in recently completed unpublished studies evaluating both indoor nitrogen dioxide levels and relative humidity in relation to respiratory symptoms, no evidence of a role for relative humidity was obtained.

When considering the disparity in the findings among these studies, a number of points must be kept in mind. Foremost is that any effect of nitrogen dioxide in potentiating acute upper respiratory infection is likely to be relatively small in relation to the totality of this disease. The common cold and related disorders would occur in large numbers even were nitrogen dioxide completely absent from our atmosphere. The inherent variation in the spectrum of illnesses defined as respiratory tract infections makes it difficult to detect a potential enhancing factor unless such a factor has a substantial impact on total incidence. However, even a factor contributing to less than 1% of total acute respiratory tract infections has an impressive numerical impact on health statistics and costs in view of the overall public health importance of such diseases.

One can, in essence, consider two types of approaches to lessening the uncertainties in detection of a factor enhancing a small percentage of total respiratory problems, although they really are part of a continuum. On the one hand, the investigator can intensively evaluate each subject in a study, including frequent very detailed questionnaires, validation of any reported findings, and meticulous attention to the actual dose of nitrogen dioxide. The logistics associated with such an extensive and expensive approach severely limit numbers and hence the statistical power. Alternatively, one can focus on increasing the numbers studied at the cost of a somewhat greater degree of uncertainty for each measure of dose or response.

To some extent, the studies of Keller et al.[11,12] can be considered to have the most intensive evaluation of its subjects, including repetitive data gathering over a reasonably long period. However, it is clearly limited by the relatively small numbers tested, particularly of school children who represent the apparent major population at risk. In contrast, studies by Melia et al.[15-18] and Speizer et al.[13,14] have the distinct advantage of a much larger number of participants and an assessment directed primarily at school children. Discrepancies do exist between the Speizer et al. and Melia et al. studies as well, a major one being whether pulmonary function tests demonstrated differences between gas and electric homes.

Another point leads one to question the generalizability of the negative findings of Keller et al.[11,12] This is the relatively low levels of nitrogen dioxide reported in the upper middle class homes tested. Obviously, it is more difficult to observe a low-level dose effect, particularly if only small numbers are evaluated. The studies of Melia and her colleagues in Middlesborough evaluated relatively lower class homes in which nitrogen dioxide levels were much above those reported by Keller et al. or by Speizer et al., again from a small sample.[10] Of note is that most studies measuring indoor nitrogen dioxide levels in the United States have looked at better grades of housing and have reported far lower levels of kitchen nitrogen dioxide than those observed in Middlesborough. A more thorough evaluation of indoor nitrogen dioxide levels in different American housing is necessary, particularly in view of decreased ventilation due to energy conservation measures.

In my judgment, the available findings can be tentatively interpreted as follows. Reasonably strong evidence associates the use of a gas stove for cooking with a small but statistically significant risk of potentiating acute respiratory tract infections. Sufficient information at least implicates nitrogen dioxide as the causative agent in enhancing pulmonary infections, but there is no definitive proof that this is the factor associated with gas stoves responsible for such an effect. Obviously, more information on this subject is needed. Of course, such a call for further scientific study is the usual end of a review of this type. In this case I believe we can realistically anticipate significant improvement in our understanding of this problem within the next few years, particularly now that the boundaries of the problem have been relatively clearly defined.

Questions and Answers

MR. HARVEY SACHS (Princeton University): What would be the relative contribution to illness of gas stoves compared to other common risks in the household, such as second-hand smoking? How does one refer to the risk to a child of parental smoking versus use of a gas stove or other normalizing variables?

DR. GOLDSTEIN: Based on the studies which are comparable, I think that cigarette smoking in the home is a greater risk to a child than using a gas or electric stove. The British have had very little difficulty in their large cohort studies picking up an effect of parental cigarette smoking on children, but they have had a fair amount of difficulty, as you could see, identifying the NO_2 effect.

MR. SACHS: Are you speaking of an order of magnitude or a factor of two?

DR. GOLDSTEIN: I think at this point, as you end up with a situation where we still have some lingering doubt as to whether or not there really is an NO_2 effect and no lingering doubt that there is a cigarette smoking effect, then the order of magnitude can be up to infinity, obviously. I would rather not try to even guess at that unless I had a chance to look through the data comparatively. When I studied this, I did not look at it from that point of view. But, clearly, cigarette smoking at home is to be avoided.

DR. DEMETRIOS MOSCHANDREAS (GEOMET Technologies, Inc.): I feel an overwhelming need to defend my statement, but I shall start by correcting my statement. I was looking for NO_2 personal monitors which would provide hourly exposure. I have talked with Dr. Palmes, and, indeed, his tube is now commercially available. I have talked with the company that manufactures it, and they both assured me that it is not the proper instrument to use. You are correct, when it comes to longer-term exposure the tube is available, and it is a very good instrument to use.

DR. GOLDSTEIN: Thank you. I am perhaps a little sensitive about this. Dr. Palmes had this idea a long time ago and had a difficult time selling it to the Environmental Protection Agency and other places because it was so cheap. They instead funded a telemetered device with a child wearing a 10 kg. pack on his back rather than this minor little item that was delayed a number of years in its production for that reason.

DR. MOSCHANDREAS: The principle is now used, and they are trying to develop a short-term exposure.

DR. GOLDSTEIN: The principle actually is the Fick principle, which was developed in the 19th century, so that is one of the reasons it was not very glamorous to do it this way.

MR. JAMES REPACE (Environmental Protection Agency): I seem to recall, in the Keller study, a statistically significant difference in the wheezing in children from gas stoves as opposed to electric stoves. There was a greater amount of wheezing in children from gas stoves.

DR. GOLDSTEIN: I do not remember whether there was wheezing or not. There was one symptom that was associated, but I tried to allude to that problem when I pointed out that one of them was positive in the other direction.

If you ask 20 questions that are really the same — in other words, wheezing, coughing, eyes tearing, etc. — and if you use a P of 0.05 as a statistical criterion, 0.05 is one chance in 20. By definition, one of them has got to be right. Keller himself describes his work very carefully and shows that he would have expected, from the number of questions he asked, that there would have been two positive associations, two statistically significant associations. He got three, and they went in different directions, and so he really did not think there was anything. And I think he is correct. I do not think that his data show anything positive at all.

DR. FERRAND: In the combustion products in the gas stove, has anyone made any in-depth investigation of the relationships between carbon monoxide, NO, NO_2, and even particulates and formaldehyde?

DR. GOLDSTEIN: Trying to look to see if there is some sort of synergistic effect?

DR. FERRAND: Yes. Depending upon the adjustments of the burner, there is quite a range in the kind of pollutants generated, even formaldehyde, for example. I wonder if those other pollutants have been considered in any of these studies.

DR. GOLDSTEIN: They have not been considered in the studies. They certainly have been considered in talking about what ought to be done next. One of the big problems we have is the kind of analytical technique we need for formaldehyde and other aldehydes. We are faced with the kind of thing we have with some of the other pollutants. Probably the easiest aldehyde to measure will not be the one that is the most damaging, because a whole series of aldehydes are formed, and we really do not know where to start. If there is a good way of measuring aldehydes, the British group that has been looking at this would be happy to start measuring them in their studies.

I think, with all respect to the organizers here, who I think are doing a very important thing — we are just touching the surface of an enormous problem that we just do not have answers to. Those in occupational medicine know that any new building is associated with a whole host of these types of symptoms. But, except for throwing around big words like aldehydes and special names, we really don't know what is causing these symptoms at all.

DR. FERRAND: I can second that. We are continually investigating problems such as you were referring to and not finding any answers.

REFERENCES

1. Ehrlich, R.: Effect of air pollutants on respiratory infection. *Arch. Environ. Health 6:*638-42, 1963.
2. Ehrlich, R.: Effect of nitrogen dioxide on resistance to respiratory infection. *Bacteriol. Rev. 30:*606-14, 1966.
3. Henry, M.C., Ehrlich, R., and Blair, W. H.: Effect of nitrogen dioxide on resistance of squirrel monkeys to Klebsiella pneumoniae infection. *Arch. Environ. Health 18:*580-87, 1969.
4. Henry, M.C., Findlay, J., Spangler, J., and Ehrlich, R.: Chronic toxicity of NO_2 in squirrel monkeys. III. Effect on resistance to bacterial and viral infection. *Arch. Environ. Health 20:*566-70, 1970.
5. Ehrlich, R. and Henry, M. C.: Chronic toxicity of nitrogen dioxide. I. Effect on resistance to bacterial pneumonia. *Arch. Environ. Health 17:*860-65, 1968.
6. Goldstein, E., Eagle, M.C., and Hoeprich, P.: Effect of nitrogen dioxide on pulmonary bacterial defense mechanisms, *Arch. Environ. Health 26:*202-04, 1973.
7. Amoruso, M.A., Witz, G., and Goldstein, B. D.: Decreased superoxide anion radical production by rat alveolar macrophages following inhalation of ozone or nitrogen dioxide. *Life Sci. 28:*2215-21, 1981.
8. Wade, W.A., III Cote, W.A., and Yocum, J. E.: A study of indoor air quality. *J. Air Poll. Control Assoc. 25:*933-39, 1975.
9. Palmes, E. D., Gunnison, A. F., Dimattio, J., and Tomczyk, C.: Personal samplet for nitrogen dioxide. *Amer. Indst. Hyg. Assoc. J. 37:*570-77, 1976.
10. Goldstein, B.D., Melia, R.J.W., Chinn, S., et al.: The relation between respiratory illness in primary schoolchildren and use of gas for cooking. II. Factors affecting nitrogen levels in the home. *Int. J. Epidemol. 8:*339-45, 1979.
11. Keller, M.D., Lanese, R.R., Mitchell, R. I., and Cote, R. W.: Respiratory illness in households using gas and electricity for cooking. I. Survey of incidence. *Environ. Res. 19:*495-503, 1979.
12. Keller, M.D., Lanese, R. R., Mitchell, R. I., and Cote, R. W.: Respiratory illness in households using gas and electricity for cooking. II. Symptoms and objective findings. *Environ. Res. 19:*504-15, 1979.
13. Speizer, F.E., Ferris, B., Jr., Bishop, Y. M. M., and Spengler, J.: Respiratory disease rates and pulmonary function in children associated with NO exposure. *Amer. Rev. Resp. Dis. 121:*3-10, 1980.
14. Speizer, F. E., Ferris, B., Jr., Bishop, Y. M. M., and Spengler, J.: Health Effects of Indoor NO_2 Exposure. Preliminary Results. In: *Nitrogen Oxides and Their Effects on Health.* Lee, S.D., editor. Ann Arbor, Michigan, Ann Arbor Science Publishers, 1980, pp. 343-59.
15. Melia, R. J. W., du V. Florey, C., Altman, D. G., and Swan, A. V.: Association between gas cooking and respiratory disease in children. *Brit. Med. J. 2:*149-152, 1977.
16. Melia, R. J. W., du V. Florey, C., and Chinn, S.: The relation between respiratory illness in primary schoolchildren and the use of gas for cooking. I. Results from a national survey. *Int. J. Epid. 8:*333-38, 1979.
17. du V. Florey, C., Melia, R. J. W., Chinn, S., Goldstein, B. D., Brooks, A. G. F., John, H. H., Craighead, I. B., and Webster, X.: The relation between respiratory illness in primary schoolchildren and the use of gas for cooking. III. Nitrogen dioxide, respiratory illness and lung infection. *Intl. J. Epid. 8:*347-53, 1979.
18. Melia, R. J. W., du V. Florey, C., Darby, S. C., Palmes, E. D., and Goldstein, B. D.: Differences in NO_2 levels in kitchens with gas or electric cookers. *Atmos. Environ. 12:*1379-81, 1978.
19. Bouhuys, A., Beck, G. L., and Schoenberg, J. B.: Do present levels of air pollution outdoors affect respiratory health? *Nature 276:*466-71, 1978.
20. Mitchell, C. A., Schilling, R. S. F., and Bouhuys, A.: Community studies of lung disease in Connecticut: Organization and methods. *Am. J. Epid. 103:*212-25, 1976.